

Research News

Database Created to Supplement Commercial Microarray Coverage of Addiction-Related Genes

Genome-wide association studies (GWAS), which scan the entire genome to find genetic variations (called SNPs) that are associated with particular diseases, have revolutionized the way scientists search for genetic causes of diseases, including drug and alcohol addiction. Most SNP research uses commercial microarrays, called 'gene chips,' which contain thousands of small pieces of DNA that recognize and bind to specific sequences of DNA in an experimental sample. Although a single gene chip can contain tens of thousands of small pieces of DNA, no chip can cover the entire human genome, and commercial chips tend to provide better coverage of some genomic regions than others. To test how well commercial microarrays include genes suspected to play a role in drug and alcohol addiction, researchers funded by NIDA first assembled a list of 910 genes known or suspected to be associated with addiction and found that commercial microarrays did not completely cover the possible SNPs found in these genes; for some genes, this lack of coverage was substantial. For example, a gene called CDH13, whose products activate a number of addiction-related signaling pathways in the brain, has 2,414 SNPs that are common in the African sample of the International HapMap project. However, only 50 percent of these SNPs were found on one of the commercial microarrays sampled. To supplement this incomplete coverage by commercial microarrays, the researchers developed a publicly available database for addiction researchers containing SNPs for the 910-gene set. All SNPs in the database are tagged with a prioritization score, which is intended as a measure of biological relevance to addiction. "Addiction researchers should find [the new database] to be a valuable tool, both in the design and interpretation stages of a GWAS," conclude the authors.

Saccone SF, Bierut LJ, Chesler EJ, Kalivas PW, Lerman C, Saccone NL, Uhl GR, Li CY, Philip VM, Edenberg HJ, Sherry ST, Feolo M, Moyzis RK, Rutter JL. Supplementing high-density SNP microarrays for additional coverage of disease-related genes: addiction as a paradigm. *PLoS One*. 2009;4(4):e5225. Epub 2009 Apr 21.

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Two Thirds of Injection Drug Users in Tijuana, Mexico Have a Latent Tuberculosis Infection

Tuberculosis (TB) is more common in Mexico than in the U.S., and active TB infection can greatly increase the risk of death in HIV-positive individuals. And while HIV prevalence in Mexico is low overall, cities on the border of the U.S. and Mexico have higher rates of HIV infection. Therefore, it is important to understand the intersection of the TB and HIV epidemics on the U.S.-Mexico border. For this reason, researchers funded by NIDA performed

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laboratory analysis of TB infection and HIV status in 1,020 injection drug users recruited between 2006 and 2007 in Tijuana, Mexico. All participants were recruited using respondent-driven sampling, which uses the peer networks of early participants to recruit additional volunteers. Four percent of the IDUs tested positive for HIV, and approximately two-thirds (681) of the IDUs tested positive for latent (inactive) tuberculosis infection (LTBI).

Fifty-four percent of the HIV-positive participants also tested positive for TB, either latent or symptomatic. An increasing number of years injecting drugs and longer residence in Tijuana were both associated with higher prevalence of LTBI. Participants who mostly injected drugs at home instead of outside the home or who spoke English at home had decreased odds of having an LTBI. Understanding the populations at risk for co-infection with HIV and TB is crucial to help control both diseases, explain the authors. "Our findings underscore the urgent need for TB screening and LTBI treatment for populations at risk for HIV infection to mitigate the potential collision between the TB and HIV epidemics in this region," conclude the authors.

Garfein RS, Lozada R, Liu L, Laniado-Laborin R, Rodwell TC, Deiss R, Alvelais J, Catanzaro A, Chiles PG, Strathdee SA. High prevalence of latent tuberculosis infection among injection drug users in Tijuana, Mexico. *Int J Tuberc Lung Dis*. 2009 May;13(5):626-32.

Many School Districts Have Punitive Responses to Positive Results from Random Drug Testing

Studies have estimated that about 14 percent of U.S. school districts containing high schools conduct suspicionless random drug testing (SRDT)—drug testing performed randomly whether or not selected students have shown any signs or symptoms of substance use. To better understand these school districts' responses to students' first positive SRDT, researchers funded by NIDA surveyed 205 of these school districts. Of the 162 districts included in the final analysis, most responded to initial positive drug tests by requiring parents to meet with school officials (88.4 percent of districts) or requiring the student to participate in a drug education, counseling, or treatment program (60.8 percent). However, many districts also

{ researchers funded by NIDA surveyed 205 of these school districts

included punitive responses to a first positive SRDT such as suspending students from extracurricular activities (66.5 percent) or school (31 percent). Almost half of the surveyed school districts (45.1%) notified law enforcement officials of a test result, which constitutes a

violation of confidentiality and "constitutes a serious breach of protocol," state the authors. Suburban schools were more likely than others to suspend students from athletic teams upon a first positive drug test, and schools in low-poverty districts (where fewer than 15 percent of students were eligible for a free or reduced-price lunch) were more likely to expel students upon a first positive drug test. The authors caution that some districts' substance use prevention coordinators may have confused their districts' responses to a first positive test from SRDT with those for subsequent positive tests, or responses to a 'for cause' test (testing conducted when there is reason to believe a student has been using drugs), both of which would likely have more severe consequences. Considering the prevalence of drug testing in schools, the authors recommend better communication of current best practices as well as expanded training and technical assistance for administrators and their school districts.

Ringwalt C, Vincus AA, Ennett ST, Hanley S, Bowling JM, Yacoubian GS Jr, Rohrbach LA. Responses to positive results from suspicionless random drug tests in US public school districts. *J Sch Health*. 2009 Apr;79(4):177-83.



Highly Selective Compounds Developed to Target the Brain's Dopamine D3 Receptor

Drug addiction is a chronic relapsing brain disease, and the discovery of effective medications to treat addictive disorders is a high priority in addiction research. A type of receptor in the brain called the dopamine D3 receptor has received significant attention from scientists as a potential target of medications to treat drug addiction. For example, in animal studies, D3 antagonists (compounds that bind to and block the activity of the receptor) were able to inhibit cocaine seeking in rodents and reduce cue-induced and stress-induced relapse to drug use. However, existing compounds that bind to the D3 receptor are not acceptable for testing in humans due to several reasons, including a lack of selectivity (they bind to other receptors in the brain in addition to the D3 receptor, with potential unwanted effects), low bioavailability (a small amount of compound actually reaches the target) and potential toxicity. To improve on the existing compounds that target D3, investigators led by NIDA's Intramural Research Program modified several promising compounds—all of the new compounds were highly selective for the D3 receptor. In fact, several of the altered compounds were 145-fold to 400-fold more likely to bind to D3 than to other dopamine receptors. Most of these compounds also had characteristics that would make them likely to be able to cross the blood-brain barrier, and therefore reach the brain. These compounds would be appropriate for future in vivo testing as potential

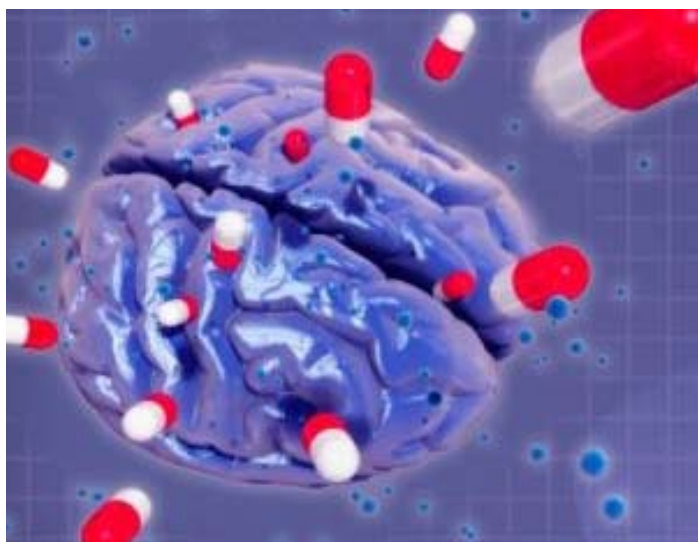
treatments for drug addiction, and may also be useful in basic science research to better understand the characteristics of dopamine D3 receptors, conclude the authors.

Newman AH, Grundt P, Cyriac G, Deschamps JR, Taylor M, Kumar R, Ho D, Luedtke RR. N-(4-(2,3-dichloro- or 2-methoxyphenyl) piperazin-1-yl)butyl)heterobiarylcarboxamides with functionalized linking chains as high affinity and enantioselective D3 receptor antagonists. *J Med Chem.* 2009 Apr 23;52(8):2559-70.

Increasing Glutamate Transmission Eliminates Cocaine-Induced Place Preference in Rats

Individuals addicted to drugs of abuse develop strong associations between the pleasurable feelings induced by the drugs and the environments associated with their drug use. These associations can serve as powerful cues that can lead to drug craving and relapse. Understanding the underlying neurobiological mechanisms that influence cue-induced craving may help with the development of successful treatments for addiction. Researchers funded by NIDA have tested whether increasing the activity of a particular receptor in the brain, the mGluR5 receptor, would facilitate the elimination of environmental cue-induced craving for cocaine. In these experiments, rats were trained in a conditioned place preference (CPP) model, where they were exposed to cocaine in a specific environment, and learned to prefer that environment over another when given a choice. After four days of CPP training, rats were given either an inactive vehicle or one of three increasing doses of a compound called CDPPB, which activates mGluR5 receptors. In a second set of experiments, CDPPB was given with or without additional drugs that either block the mGluR5 receptor or block other receptors called NMDA receptors (which are affected by increased mGluR5 receptor activity). Administration of CDPPB did not cause any toxic effects, and CDPPB significantly helped eliminate the rats' cocaine-induced CPP. This positive effect of CDPPB was blocked by the drugs that either blocked the mGluR5 or NMDA receptors, indicating that both of these types of receptors help mediate the association between environmental cues and drug use.

Gass JT, Olive MF. Positive allosteric modulation of mGluR5 receptors facilitates extinction of a cocaine contextual memory. *Biol Psychiatry.* 2009 Apr 15;65(8):717-20. Epub 2008 Dec 19.



Men with Anabolic-Androgenic Steroid Dependence also Have High Lifetime Prevalence of Opioid Dependence

Illicit use of anabolic-androgenic steroids (AAS) has become a widespread problem in the United States, as their use has spread from elite athletics into the general population. Studies have estimated that about 30 percent of illicit AAS users will develop AAS dependence, but little is known about how psychological attributes and history of other substance use differ between AAS users who become dependent and those who do not, or between dependent AAS users and individuals who never try AAS. To better understand these differences, researchers funded by NIDA recruited 134 experienced male weightlifters between the ages of 18 and 40 in Massachusetts and Florida and conducted detailed psychiatric evaluations. Seventy-two of the men reported never using AAS; 42 reported use but not dependence; and 20 met the criteria for AAS dependence. Overall, dependent AAS users had a significantly higher lifetime prevalence of a childhood conduct disorder and reported lower education levels than non-dependent AAS users and those that had never used AAS. Dependent AAS users, compared to non-dependent AAS users, had a longer lifetime history of steroid use (6 years versus 6 months, respectively), were also more likely to use other performance-enhancing drugs and were 6.7 times more likely to have experienced opioid abuse or dependence. Dependent AAS users were also 16.3 times more likely to have experienced opioid abuse or dependence than men who had never used AAS. Previous studies in humans have also suggested an association between AAS use and opiate use. Furthermore, animal studies have suggested that the two drug classes may affect similar neuronal pathways. These data, together with the current study, “suggest that individuals with AAS dependence and individuals with classical substance dependence may perhaps share important underlying biological and neuropsychological vulnerabilities,” conclude the authors.

Kanayama G, Hudson JI, Pope HG Jr. Features of men with anabolic-androgenic steroid dependence: A comparison with nondependent AAS users and with AAS nonusers. *Drug Alcohol Depend.* 2009 Jun 1;102(1-3):130-7. Epub 2009 Apr 1.

Benzotropine Analogs Reduce Cocaine Self-Administration in Rats

Currently, there are no FDA-approved medications for the treatment of cocaine addiction. Dopamine, a key neurotransmitter associated with motivation and pleasure, is also a key mediator of the effects of all illicit drugs on the brain. Medications that target dopamine are being developed for the potential treatment of cocaine addiction. An ideal medication targeting the dopamine pathway would reduce or block the effect of cocaine on dopamine levels in the brain and would not have any rewarding effects itself, which would increase a treatment’s own potential for abuse. Researchers from NIDA’s Intramural Research Program are testing compounds that specifically target dopamine transporters—proteins that remove dopamine from the space between cells, thereby stopping their action—as potential drugs for the treatment of cocaine addiction. In a new series of experiments, the researchers tested a class of compounds called benzotropine (BZT) analogs to see if they could reduce cocaine self-administration in rats and to test for any potentially addictive effects of the BZT analogs themselves. In these experiments, rats were taught to self-administer cocaine over several days. The researchers then substituted either one of three different BZT analogs for the cocaine during self-administration testing. Researchers found that two of the three BZT analogs that were tested significantly reduced drug self-administration behaviors (pressing of the lever that would normally release a dose of cocaine) in the animals, which indicates that those BZT analogs themselves have low potential for abuse. When given before rats had access to cocaine in the self-administration chambers, these two BZT analogs also significantly reduced the number of times the rats would press a lever to receive cocaine. The authors conclude that these compounds are promising candidates for the development of medications for cocaine addiction.

Hiranita T, Soto PL, Newman AH, Katz JL. Assessment of reinforcing effects of benzotropine analogs and their effects on cocaine self-administration in rats: comparisons with monoamine uptake inhibitors. *J Pharmacol Exp Ther.* 2009 May;329(2):677-86. Epub 2009 Feb 19.

Drug Combinations Contribute to HIV Risk in Gay and Bisexual Men

Injectable drugs such as heroin have an obvious link with HIV infection, through the sharing of contaminated drug-injection equipment. Non-intravenous drug use, however, can also increase the risk of HIV infection by impairing judgment and thereby increasing the occurrence of

Men who used all three drugs were 8 times as likely to become HIV positive

risky sexual behavior while under the influence of drugs. Researchers funded by NIDA examined the link between the use of several popular non-intravenous drugs and HIV infection in a group of 1667 initially HIV-negative gay and bisexual men. All men were part of the Multicenter AIDS Cohort Study, an ongoing prospective study of HIV infection and treatment among gay and bisexual

men in the United States. Between 1998 and 2008, the researchers tracked the men's use of inhaled nitrites ('poppers'), stimulants including methamphetamine, cocaine, crack, and ecstasy, and erectile dysfunction drugs, either prescribed or used illicitly. During the 10-year period, 57 of the men became HIV-positive. In analyses examining possible relationships between unprotected sex, drug use, and other variables associated with increased risk of HIV infection, the researchers determined that unprotected sex increased the risk of HIV infection in this group of men by 41 percent, and the use of one or more of the drugs studied increased the risk by an additional 33 percent. Men who used all three drugs were 8 times as likely to become HIV positive as men who used none of the drugs. HIV prevention interventions that target both drug use and high-risk sex are needed for this group of high-risk men, conclude the authors.

Ostrow DG, Plankey MW, Cox C, Li X, Shoptaw S, Jacobson LP, Stall RC. Specific sex drug combinations contribute to the majority of recent HIV seroconversions among MSM in the MACS. *J Acquir Immune Defic Syndr*. 2009 Jul 1;51(3):349-55.

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